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EXAMINER	
JUEDES, AMY E	

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1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/674,433	MATOSSIAN-ROGERS, ARPI	
	Examiner	Art Unit	
	Amy E. Juedes, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12,14,15 and 17-30* is/are pending in the application.

4a) Of the above claim(s) *1-10,12,14,15 and 17-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 3/15/07, are acknowledged.

Claims 29-30 have been amended.
Claims 1-10, 12, 14-15, and 17-30 are pending.

2. Claims 1-10, 12, 14-15, and 17-28 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 29-30 are being acted upon.

3. The rejection of the claims under 35 U.S.C. 112 second paragraph, as outlined in sections A), B), and D) of the previous office action, is withdrawn in view of Applicant's amendment to the claims.

4. The rejection of the claims under 35 U.S.C. 112 first paragraph for new matter, as outlined in section A) of the previous office action, is withdrawn in view of Applicant's amendment to the claims.

5. The rejection of the claims under 35 U.S.C. 102 as being anticipated by WO 92/12996 is withdrawn in view of Applicant's amendment to the claims. Specifically, WO 92/12996 does not teach administering an antibody that binds to both an anti-T cell receptor antibody and a GPI linkage epitope.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 29-30 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As set forth previously, C) Claims 29-30 are indefinite in the recitation of treating a condition where "hormonal dysregulation, hyperinsulinaemia, and/or insulin resistance are present". Specifically, it is unclear how autoimmune diseases, cancer, and cardiovascular disease can be considered conditions where "hormonal dysregulation, hyperinsulinaemia, and/or insulin resistance are present". For example, while some patients with autoimmune disease (for example type 1

diabetics) might have hyperinsulinaemia, it is unclear how all autoimmune diseases (for example, multiple sclerosis) can be classified as a condition where "hormonal dysregulation, hyperinsulinaemia, and/or insulin resistance are present". Multiple sclerosis is well characterized as a T cell mediated autoimmune disease involving an attack on the myelin sheath of the central nervous system. It is unclear how multiple sclerosis can be considered a condition where "hormonal dysregulation, hyperinsulinaemia, and/or insulin resistance are present". Likewise, the recitation of cancer covers a broad range of different diseases. While some types of cancer might involve hormonal dysregulation, hyperinsulinaemia, and/or insulin resistance, it is unclear how, for example, a brain tumor can be considered a condition where "hormonal dysregulation, hyperinsulinaemia, and/or insulin resistance are present".

E) Claim 30 is indefinite in the recitation of the conditions "pre-IDDM" and "pre-NIDDM". The specification does not define the terms, and it is not clear what characterizes a patient as having "pre-IDDM" or "pre-NIDDM". Are the claims intended to encompass treating healthy patients that may or may not develop diabetes?

Applicant's arguments filed 3/15/07 have been fully considered, but they are not persuasive.

Regarding C), Applicant argues that the claims are definite, since they are clearly limited to autoimmune diseases, cancer, or cardiovascular diseases that are also conditions where hormonal dysregulation or hyperinsulinaemia and insulin resistance are present.

It is not clear what conditions are encompassed by the instant claims. For example, are the claims intended to encompass treating multiple sclerosis or brain cancer in a patient who in undergoing menopause (i.e. a "hormonal dysregulation").

Regarding E), Applicant argues that it would be immediately evident to a skilled artisan that, in light of the specification, "pre-IDDM" and "pre-NIDDM" are the underlying metabolic disorders that precede clinical IDDM and NIDDM. Applicant has submitted several scientific abstracts as evidence of the meaning of the terms "pre-IDDM" and "pre-NIDDM".

Applicant has submitted several scientific abstracts that recite the terms "pre-IDDM" or "pre-NIDDM". However, none of the cited abstracts provide a definition of the terms. In fact, Bergman et al. state that there is a need to define an efficient representation of the "pre-NIDDM" phenotype. The instant specification does not define the terms "pre-IDDM" or "pre-NIDDM", and the references cited by Applicant indicate that the phenotype of "pre-IDDM" and "pre-NIDDM" is not clearly defined in the art. Thus, the metes and bounds of the claims cannot be established.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 29-30 stand rejected under 35 U.S.C. 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

As set forth previously, The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

B) A method of treating "pre-IDDM" or "pre-NIDDM" (claim 30).

In the Preliminary Amendments, filed 3/16/06, Applicant indicates that support for the new limitations of Claim 29 can be found at page 29 of the specification, and support for claim 30 can be found in the background information about IDDM and NIDDM at pages 4-6, and page 8.

A review of the specification fails to reveal support for the new limitations.

Regarding B), the specification does not disclose treating "pre-IDDM" or "pre-NIDDM". In fact the specification does not disclose the terms "pre-IDDM" or "pre-NIDDM". It is noted that in the remarks accompanying the preliminary amendment, Applicant argues that even though the terms "pre-IDDM" and "pre-NIDDM" are not specifically recited, the detailed description of IDDM and NIDDM includes some discussion of the development of disease, and therefore one of ordinary skill in the art would inherently recognize that the development of IDDM and NIDDM means conditions of "pre-IDDM" and "pre-NIDDM". However, it is noted that obviousness is not the standard for determining new matter, and the specification only discloses treating IDDM or NIDDM and not "pre-IDDM" or "pre-NIDDM", as now claimed.

Applicant's arguments filed 3/15/07 have been fully considered, but they are not persuasive.

Applicant argues that the specification clearly defines the term "pre-diabetes", and that "pre-IDDM" and "pre-NIDDM" are encompassed by "pre-diabetes".

The specification does not define the term "pre-diabetes", but rather discusses a particular example of prediabetic NOD mice that have normal fasting glucose and insulin levels, but markedly elevated glucagon levels. This discussion appears as

part of background information, and the instant specification does not disclose treating "pre-diabetes" with the antibody of the instant claims. Furthermore, "pre-diabetes" is represents a genus of conditions, and it is well established that the disclosure of a genus does not provide adequate support for a specific species within the genus (i.e. "pre-IDDM" and "pre-NIDDM").

Applicant further argues that the specification discloses using the antibodies "in prophylactic and therapeutic interventions of autoimmune and related diseases, including IDDM and NIDDM".

However, it is not clear that "prophylactic" treatment of IDDM and NIDDM has the same scope as treating "pre-IDDM" and "pre-NIDDM".

9. Claims 29-30 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could function to treat conditions where hormonal dysregulation or hyperinsulinaemia and insulin resistance are present by administering an antibody capable of binding an anti-T cell receptor antibody and a GPI linkage epitope, as broadly claimed.

As set forth previously, The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the

invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

With regards to the instant claims, their breadth comprises a primary issue as regards the unpredictability of the claimed method. It is not clear how the antibodies would be able to treat conditions where hormonal dysregulation, hyperinsulinaemia, and/or insulin resistance are present. The instant specification demonstrates that a particular antibody raised against an anti-TCR antibody binds to alpha cells and modulates insulin secretion. The instant specification states on pg. 36 that the injection of antibody will be designed to prevent the development of autoantibodies of the same specificity by a feedback mechanisms suppressing existing B cells, or by an idiotypic network of antibody development giving rise to protective mechanisms. However, it is noted that the instant specification does not provide any evidence that antibodies specific for an anti-TCR antibody play a pathogenic role in the broad range of conditions encompassed by the claims, and thus it is not clear how preventing the development of such antibodies would be of benefit. For example, the claims encompass in their breadth, not only treating conditions like diabetes, that directly involve an altered insulin response, but encompass treating any condition where "hormonal dysregulation, hyperinsulinaemia, and/or insulin resistance" are present. This might encompass treating menopause, thyroid disease, or even depression. Furthermore, it is noted that dependent claim 30 recites treating autoimmune disease, cancer, or cardiovascular disease, as the condition. Therefore, the claims encompass treating, for example, multiple sclerosis, brain tumors, varicose veins, aneurysm etc. The instant specification does not provide any mechanistic link as to how the insulin modulating properties of the antibodies would correlate with their ability to treat the widely different diseases and conditions encompassed by the claims.

Therefore, given the breadth of the claims and the state of the prior art, the instant specification must provide a sufficient and enabling disclosure, commensurate in scope with the instant claims. The instant specification demonstrates that a particular antibody raised against an anti-TCR antibody binds to alpha cells and modulates insulin secretion. The specification further demonstrates that antibodies that bind to anti-TCR antibody are present in 3 patients with IDDM. The conclusion drawn by Applicant appears to be that the antibodies play a pathogenic role in IDDM, and that treatment with the same antibodies can function in suppressive feedback mechanism. However, even if administering the antibodies could function to suppress the development of the same antibodies in vivo, the specification does not correlate how this would function to treat the widely divergent diseases encompassed by the claims (i.e. menopause, multiple sclerosis, brain tumors, etc.). Furthermore, even if the claims were limited to treating insulin related disorders such as diabetes, it is noted that Applicant has not provided any evidence that the antibodies found in the IDDM patients are pathogenic. For example, they have not demonstrated that the anti-anti-TCR antibodies present in vivo modulate insulin secretion or bind to alpha cells, or even that the antibodies are selectively present in IDDM patients and not in controls. Furthermore, given the fact that the claimed treatment involves administering the supposed pathogenic antibody, it seems extremely unpredictable as to whether the antibody would be able to function in a suppressive feedback mechanism, as asserted by Applicant, without itself also inhibiting insulin production and exacerbating diabetes. Moreover, the instant specification does not provide any working examples demonstrating the effectiveness of administering the antibodies to treat any disease (including diabetes). Accordingly, the method as broadly claimed must be considered highly unpredictable. Given said unpredictability, the method of the instant claims must be considered to require undue experimentation.

Applicant's arguments filed 3/15/07 have been fully considered, but they are not persuasive.

Applicant argues that the specification discloses that the anti-anti-TCR antibodies have a profound effect on insulin secretion, and are present in the serum of diabetic patients. Applicant further provides post-filing references as evidence of the efficacy of the claimed antibodies for treating diabetes.

As an initial matter, the references cited by Applicant were published in 2007, and cannot support enablement as of the filing date of the instant application. Furthermore, the cited references provide clinical data demonstrating the efficacy of a peptide derived from the CDR of an anti-anti TCR antibody. In contrast, the instant claims appear to be drawn to administering a pathogenic anti-anti-TCR antibody that cross-reacts with a GPI linkage epitope, or binding fragment thereof, to treat any condition of hormonal dysregulation or hyperinsulinaemia and insulin resistance. While a CDR peptide of a pathogenic antibody might function in a feedback mechanism to inhibit pathogenic antibody formation, no evidence is provided that administering the entire antibody would function in a similar feedback mechanism. Moreover, in contrast to a CDR peptide, administration of a pathogenic antibody might be expected to be detrimental due to its effect on insulin secretion.

Applicant further argues that it is common for potentially pathogenic agents to be used in the treatment of disease, citing in particular the asserted analogous method of administering anti-D Ig to Rh negative mothers. Applicant concludes that at an appropriate dose, as disclosed on page 36 of the specification, the pathogenic antibodies can be used to treat disease.

The instant specification does not provide any specific teaching regarding the dose of the pathogenic antibody, but rather generally states that the injection of the antibody will be designed to prevent the development of autoantibodies of the same specificity by feedback mechanisms. Furthermore, in contrast to Applicant's assertion, the instant method is not analogous to the administration of anti-D Ig to Rh negative mothers to prevent Rh sensitization. The administration of anti-D Ig functions to prevent the development of Rh specific antibodies by binding to Rh antigens on the surface of fetal red blood cells, preventing them from stimulating the maternal immune system. In contrast, the specification teaches that the instant antibodies function to suppress disease by feedback mechanisms, including the generation of protective anti-

idiotypic antibodies.

Applicant further argues that is entirely reasonable for the skilled artisan to extrapolate the findings of the instant application in diabetic patient to the broad range of disease listed in the claims, which are clearly linked by a centralized disease mechanism.

The instant claims encompass treating any condition of hormonal dysregulation (for example including menopause, conditions relating to altered testosterone, pituitary gland disorders, human growth hormone deficiency, etc.), as well as cancer, autoimmune disease, and cardiovascular disease. These conditions are not linked by a centralized disease mechanism, and it is unclear how an antibody that effects insulin secretion could be useful for treating the wide range of conditions encompassed by the claims.

10. The following are new grounds of rejection necessitated by Applicant's amendment.

11. Claims 29-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 29 is indefinite in the recitation of a glycosyl phosphatidyl inositol "(GPI linkage epitope". The claim is not clear since a parentheses is missing.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 8am - 5pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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5/11/07
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